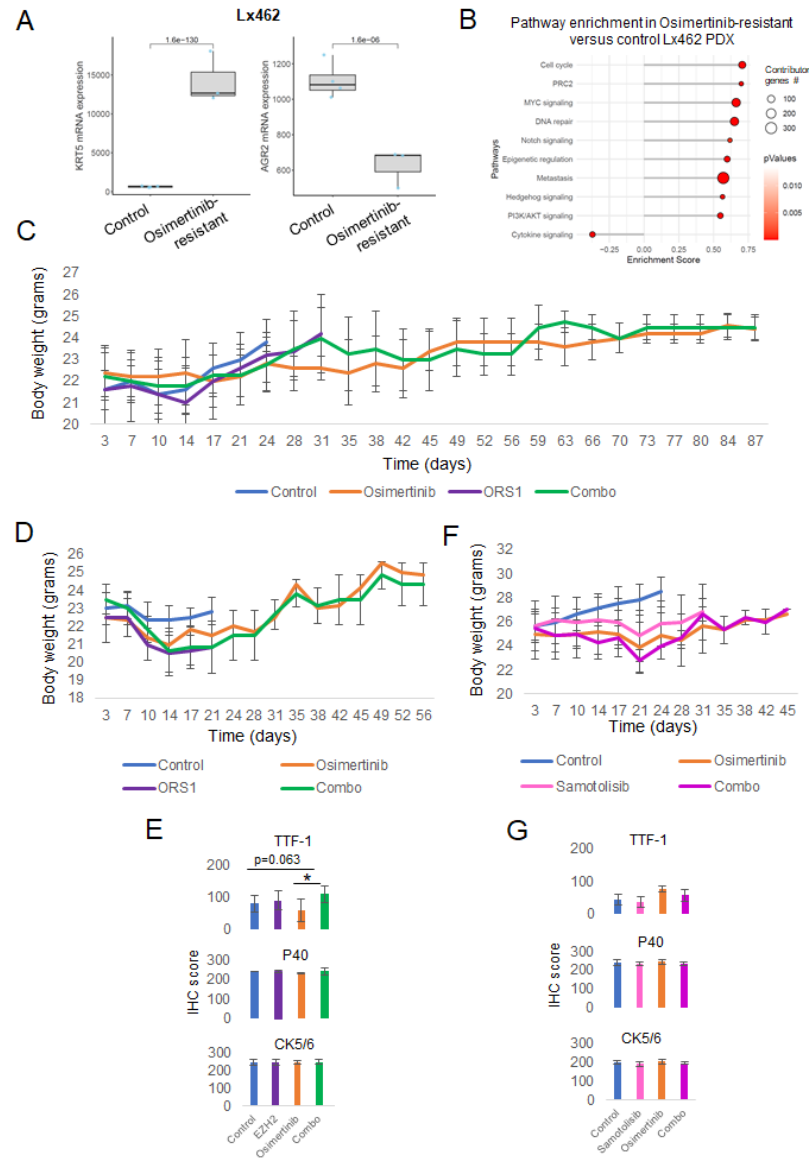


**Supplementary Figure S2.** Related to Figure 3. (A) Dot plot showing the correlation of the different LUSC subtypes with the cohorts under study. mRNA expression levels of TP63 (B) and EZH2 (C) in LUAD, T-LUAD, T-LUSC and LUSC samples in our cohort. Expression level differences were assessed by performing a two-tailed Student's t-test. p-values legend: \*  $p < 0.05$ , \*\*  $p < 0.01$





Supplementary Figure S4

**Supplementary Figure S4.** Related to Figure 7. (A) KRT5 and AGR2 expression on control and osimertinib-resistant (squamous-like) Lx462 PDX. (B) Pathway enrichment analyses on DEGs for osimertinib-resistant (squamous-like) versus control Lx462 PDX showing common dysregulated pathways with those on transforming clinical samples (see **Figure 3D**). Mouse body weight measurements of the mice bearing the treatment-naïve (C) or osimertinib-resistant (D) Lx462 PDX tumors treated with osimertinib, ORS1 or their combination. (E) Barplots showing IHC quantification of TTF-1, P40 and CK5/6 stains in the control and osimertinib-, ORS1- and combination-treated groups (mean  $\pm$  SEM score values per group are shown). (F) Mouse body weight measurements of the mice treated with osimertinib, samotolisib and their combination. (G) Barplots showing IHC quantification of TTF-1, P40 and CK5/6 stains in the control and osimertinib-, samotolisib- and combination-treated groups (mean  $\pm$  SEM score values per group are shown). Expression level differences were assessed by performing a two-tailed Student's t-test. p-values legend: \*  $p < 0.05$ .